Remarks

Claims 1-48, 57-62, 64, and 68-75 were pending in the subject application. By this Amendment, claims 57, 58, and 60-62 have been amended, claims 1-48, 68-75 have been canceled, and new claims 76-86 have been added. The undersigned avers that no new matter is introduced by this amendment. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 57, 58, 60-62, 64, and 76-86 are currently before the Examiner for consideration, and favorable consideration of these claims is respectfully requested.

The applicants gratefully acknowledge the Examiner's withdrawal of the rejections under 35 U.S.C. §112, second paragraph, and 35 U.S.C. §103.

Initially, the Office Action indicates that the Information Disclosure Statement (IDS) received by the Patent Office on February 20, 2001 (paper no. 3; which was submitted by the applicants on February 14, 2001) cannot be considered because it fails to comply with 37 C.F.R. §1.98(a)(1) because the document was not accompanied by a PTO-1449 form. The applicants respectfully submit that the IDS was accompanied by the PTO-1449 form, as evidenced by a copy of the return receipt post card the applicants received from the Patent Office (which is attached herewith). However, the outstanding Office Action was accompanied the subject PTO-1449 form, which was initialed by the Examiner, rendering the issue moot.

By this Amendment, the cross-reference section of the specification has been updated to reflect that international application no. PCT/GB96/02251 has been published as WO 97/10329 on March 20, 1997.

The Office Action indicates that the applicants have not filed certified copies of the priority documents, namely international application no. PCT/GB/02251 and Great Britain application no. GB 9518606.0. As an initial matter, the applicants respectfully submit that a claim to foreign priority under 35 U.S.C. §119 is not made to international application no. PCT/GB/02251. Rather, the subject application is a continuation of an application that is a continuation of a national phase application of PCT/GB/02251. The Declaration of record and the Claim of Priority under 35 U.S.C. §119 submitted on November 14, 2001 indicate that foreign priority is claimed to Great Britain

application no. GB 9518606.0. Furthermore, the applicants respectfully direct the Examiner's attention to Rule 17.2 of the Patent Cooperation Treaty, which states:

> (a) Where the applicant has complied with Rule 17.1(a) or (b), the International Bureau shall, at the specific request of the designated Office, promptly but not prior to the international publication of the international application, furnish a copy of the priority document to that Office. No such Office shall ask the applicant himself to furnish it with a copy. (emphasis added)

The PCT procedure concerning priority documents is explained in MPEP 1828 and 1893.03(c). The applicants respectfully submit that the priority documents were submitted to the International Bureau in compliance with PCT Rule 17.1 and the priority documents were, in turn, provided to the U.S. Patent Office, as a designated office, by the International Bureau. Receipt of the certified priority documents by the U.S. Patent Office is acknowledged in the Notice of Acceptance of Application that the applicants received from the U.S. Patent Office in the parent application (U.S. serial no. 09/043,061), a copy of which is submitted herewith. Therefore, the applicants respectfully submit that they are not required to submit certified copies of the priority documents to the U.S. Patent Office.

The Office Action indicates that a substitute Declaration with priority claims to U.S. application serial no. 09/672,606, U.S. application serial no. 09/043,061, international application no. PCT/GB96/02251, and Great Britain application no. GB 9518606.0 is required. 37 C.F.R. §1.63(d)(1) states that a newly executed oath or declaration is not required under 37 C.F.R. §1.51(b)(2) and §1.53(f) in a continuation or a divisional application, provided that the requirements of 37 C.F.R. §1.63(d)(1)(i) through (iv) have been met, as they have in the subject application. The application is a continuation of U.S. application serial no. 09/672,606, which is a continuation of U.S. application serial no. 09/043,061. A copy of the Declaration submitted in both application serial no. 09/672,606 and application serial no. 09/043,061 was filed with the subject application on January 12, 2001. As indicated in MPEP 602.05(a), "a copy of an oath or declaration from a prior application may be submitted with a continuation or divisional application even if the oath or declaration identifies the application number of the prior application." Therefore, the applicants respectfully submit that there is no requirement to submit an "updated" Declaration to the Patent Office.

By this Amendment, the applicants have amended claims 57, 58, and 60-62, and added new claims 76-86. Support for these amendments and the new claims can be found throughout the subject specification and claims as originally filed. The applicants have amended claim 57 to recite a method for treating a disorder associated with damage to, or loss of, brain cells in a mammal, by intracerebrally transplanting pluripotent, nestin-positive neuroepithelial cells into the brain of the mammal, wherein the cells have been genetically modified to be conditionally immortal, wherein the cells are immortal prior to transplantation and differentiate after transplantation, and wherein the transplantation improves brain function of the mammal. Support for this amendment, the amendments of claims 58 and 60-62, and new claims 76-86 can be found, for example, at page 1, lines 25-36, page 2, lines 1-10 and 14-24, page 5, lines 32-36, page 6, page 7, lines 1-7, page 9, lines 1-15 and 30-36, page 10, lines 1-36, page 12, lines 10-23, page 14, lines 5-11 and 29-32, page 17, lines 21-36, page 18, page 19, lines 1-32, page 20, lines 27-36, and page 21, lines 1-8, of the subject specification and claims as originally filed.

Claims 57-62, 64, and 68-75 are rejected under 35 U.S.C. §112, first paragraph, as lacking sufficient written description. The applicants respectfully submit that the subject specification provides a sufficient written description of the claimed subject matter.

The Office Action states that the subject specification teaches using mouse cells to restore cognitive function and suggests the use of human cells isolated at about eight weeks gestation. The Office Action cites the Gray *et al.* publication (pages 1409-1409) as showing that the isolation of suitable cells must be taken at fifteen weeks gestation, and that this is essential to obtain the required amount of differentiation. However, the passage in the Gray *et al.* publication relied on by the Examiner concerns an overview of conventional transplantation methods using fully differentiated cells, not the pluripotent nestin-positive cells used in the method of the invention. Therefore, the applicants respectfully submit that the Examiner's interpretation of the teaching of Gray *et al.* is incorrect. The subject specification teaches that cells should be isolated early enough in the developmental pathway that they retain the ability to differentiate into the desired brain cell phenotypes (page 13, lines 7-11). It is well known by those skilled in the art that the plasticity (*e.g.*, pluripotency) of embryonic cells is generally inversely related to the age of embryonic development. Therefore, if nestin-positive pluripotent cells are obtainable from a human at 12 weeks gestation, it

is at least as likely, if not more likely, that the cells would be obtainable from a human at an earlier stage of development, *e.g.*, 8 weeks gestation. As indicated at page 13, lines 5-7 of the specification, the region of the brain from which neuroepithelial cells are obtained and the precise time (stage and development) they are obtained may vary. The Declaration under 37 C.F.R. §1.132 by Dr. Sinden, which accompanied the Amendment submitted on September 30, 2002, shows that pluripotent nestin-positive neuroepithelial cells can be obtained from human fetal cortex at 12 weeks gestation (see paragraph 9 and Exhibit D of the Declaration).

Thus, page 13, lines 5-16, of the specification highlights 8 weeks as an example of when such pluripotent cells can be isolated. The human cells can also be isolated at 12 weeks (as demonstrated by Exhibit D) and even later, depending on the brain region. As will be appreciated by one of ordinary skill in the art, the hippocampus and cortex are properly identifiable as anatomical structures at approximately 10-12 weeks, which is why the human cells were isolated at the 12-week gestation period. The cells described in Exhibit D were taken from the cortex because the cells are readily obtainable in large numbers from this brain region. The success of the experiment described in Exhibit D using cortex cells supports the teaching of the specification; pluripotent neuroepithelial cells other than hippocampal cells are capable of improving a brain disorder, such as cognitive deficit. Once obtained, cells can then be screened *in vitro* to verify their ability to differentiate upon transplantation, as taught at page 13, lines 17-18, and Example 4, at pages 20-21 of the specification. The Examiner has provided no reasons to doubt that the claimed cells can be obtained from more than one region of the brain or more than one gestational stage.

The Office Action also cites the Villa *et al.* publication as showing that properties identifying human neural stem cells is not well understood. The applicants respectfully submit that the Villa *et al.* publication supports the written description of the claimed subject matter in that it shows that one of ordinary skill in the art can obtain cells having the properties that the specification teaches are desirable. The Villa *et al.* publication is concerned with defining the optimal conditions for preparing suitable pluripotent cells and makes various statements that genetically-modified cells provide the most convenient method. The cells used in the Villa *et al.* publication are taken at approximately ten weeks gestation. Furthermore, the Villa *et al.* publication makes it clear that suitable cells can be defined in terms of nestin expression and pluripotency. These are the conditions

that are referred to in the specification and recited in the claims of the subject application. Although there is a statement in the Villa *et al.* publication that properties identifying a human neural stem cell are not well understood, this does not mean that a human neuroepithelial pluripotent cell cannot be identified. Clearly, Villa *et al.* and others in the art have done so.

At page 6, lines 6-11, the Office Action concludes that properties other than pluripotency and expression of nestin are required to identify the recited cells. However, the applicants respectfully submit that the Office Action does not provided a rationale to support the assertion. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

Claims 57-62, 64, and 68-75 are rejected under 35 U.S.C. §112, first paragraph, as non-enabled. The applicants respectfully submit that the subject specification fully enables the claimed subject matter.

The Scheffler *et al.* publication (*Trends in Neurosci.*, Vol. 22, pg. 348-357, 1999) has been cited in the outstanding Office Action and earlier Actions as showing that it was "unpredictable" how to target particular areas of the brain when transplanting neural cells. However, the relevant passage in the Scheffler *et al.* publication refers to a study that used transplanted post-natal and adult neurons, and did not relate to the transplantation of conditionally immortal pluripotent neuroepithelial cells. As indicated in the Sinden Declaration, "one of the great advantages of the present invention is that it is not necessary to target particular areas of the brain to correct cell damage." This is emphasized at various points throughout the subject specification, as well (see, for example, page 5, lines 10-31). As Dr. Sinden explains in his Declaration, "previously, it was thought that to treat damage in a developed postnatal or adult brain, it was necessary to use tissue/cells derived from the same area as that damaged. Importantly, prior to our invention, even if the cells to be transplanted were taken from a fetus, ... the cells would typically be committed to a particular phenotype. Moreover, prior to our work, there was no selection of nestin-positive, pluripotent cells, or genetic modification of the cells to confer conditional immortality such that the cells would be immortal prior to transplantation but differentiate subsequent to transplantation." In contrast, applicants realized that, "surprisingly, transplanting cells that were selected to retain a nestin-positive, pluripotent, conditionally immortal phenotype resulted in the repair of damage, and this was

independent of the site of damage", as indicated in Dr. Sinden's Declaration. Accordingly, using the cells of the claimed invention permits treatment at different sites of damage with one cell line, which is selected on the basis of its nestin-positive, pluripotent characteristics, and is genetically modified to be conditionally immortal.

In contrast to the observations made in the Scheffler *et al.* publication, as stated above, the applicants have shown that the targeting of cells is not necessary using the cells of the subject invention. The subject specification teaches that the cells migrate to areas of damage after transplantation, become integrated in the damaged areas, effecting repair. As explained by Dr. Sinden in his Declaration, "this ability of the cells to migrate (which we were the first to observe) is an inherent feature of the cells; therefore, the difficulties identified in the Scheffler *et al.* publication will not be experienced when using nestin-positive, pluripotent neuroepithelial cells that have been genetically modified to be conditionally immortal."

It is well settled patent law that an applicant's statements must be accepted as true unless the Patent Office can provide evidence to doubt the truth of those statements. *In re Marzocchi*, 169 USPQ 367 (CCPA 1971). The Examiner has not provided acceptable reasoning for doubting these statements. The record is replete with evidence supporting the truth of the specification's teachings that the cells of the invention migrate to areas of damage after transplantation, become integrated within the damaged brain, and achieve repair.

Submitted with the Sinden Declaration as Exhibit B was a copy of U.S. Patent Application Publication No. 2002/0037277 (now U.S. Patent No. 6,569,421). The example at pages 2-5 of the published application clearly demonstrates the migration of the cells, and also shows that cells from one region of the brain (hippocampal region) can repair damage to a different area of the brain, such as cortex and basal ganglia. The cells utilized in the example of Exhibit B are nestin-positive, pluripotent neuroepithelial cells that have been genetically modified to be conditionally immortal, as recited in the currently pending claims. As indicated in the Sinden Declaration, "compelling evidence of extensive migration is presented at page 4, paragraph 0047, which indicates that contralaterally grafted cells 'migrated across the midline to the opposite side of the brain (emphasis added)'."

The Snyder *et al.* patent (U.S. Patent No. 6,528,306), which is submitted herewith, describes

the migratory properties of neural stem cells and demonstrates that the cells can be maintained in culture in an undifferentiated state, with differentiation occurring upon transplantation. The background section of the Snyder *et al.* patent cites several early scientific papers in support of this. For example, at column 1, lines 44-56, the Snyder *et al.* patent indicates that neural stem cells are extremely plastic and can migrate and differentiate "in a temporally and regionally appropriate manner ..., responding similarly to local microenvironmental cues for their phenotypic determination and appropriately differentiating into diverse neuronal and glial cell types."

The applicants submit that, given the benefit of the specification's disclosure, a person of ordinary skill in the art could readily identify and use nestin-positive, pluripotent neuroepithelial cells as claimed. Evidence of the ability to use a variety of pluripotent, nestin-positive neuroepithelial cells to treat various tissues is provided within Exhibit D, as described above. Exhibit D describes an experiment carried out using human nestin-positive pluripotent neuroepithelial cells derived from the human fetal cortex, to treat damage associated with the basal forebrain. These cells were genetically modified to be conditionally immortal, as recited in the currently pending claims. As indicated above, the applicants respectfully submit that the teachings of the specification and Exhibit D are consistent, and the human nestin-positive neuroepithelial cells described in Exhibit D correlate with the teachings of the subject specification as originally filed. As indicated at page 13, lines 5-7, the region of the brain from which neuroepithelial cells are obtained and the precise time (stage and development) they are obtained may vary.

The Sinden *et al.* publication (*Neuroscience*, 81:599-608, 1997) has been cited in the outstanding Office Action and previous Actions as suggesting that CA1 cells derived from the hippocampus must be used to repair damaged CA1 hippocampal tissue. The applicants submit that the cited portion of the Sinden *et al.* (1997) reference is merely characterizing the prior art. As indicated in the Sinden Declaration, "the statement referred to by the Reviewer within the Sinden *et al.* publication (of which I am the first author), is made with respect to a previous study that used primary cells that were mature, differentiated or committed CA1 cells, and not the conditionally immortal, pluripotent, nestin-positive, neuroepithelial cells that are used in the method of our invention" (emphasis added).

As indicated in the Sinden Declaration, "provided the neuroepithelial cells are nestin-positive

and retain the ability to differentiate into the specified phenotypes in response to environmental signals, they are appropriate for use in the present invention." The Scheffler *et al.* publication does not provide any reason to doubt that one of ordinary skill in the art, having the benefit of the specification's disclosure, can determine what is, and what is not, an appropriate pluripotent neuroepithelial cell for use in the subject invention.

While the applicants acknowledge that some experimentation and screening may be required to isolate human, pluripotent, nestin-positive neuroepithelial cells, the court in *In re Wands* has stated

Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue' not 'experimentation'.

> The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

The cells recited in the claimed methods are positive for the progenitor cell marker, nestin. As indicated in the Sinden Declaration, "nestin-positive cells can be readily identified using immunocytochemistry," as described at pages 20 and 21 of the subject patent application, or by other techniques known to those of ordinary skill in the art. Furthermore, Example 4 of the specification describes an *in vitro* screening method for determining the pluripotency of the cells *in vivo* (see page 13, lines 23-26). The experimentation and screening required to obtain the necessary pluripotent, nestin-positive neuroepithelial cells are standard and routine in the art. Thus, the applicants respectfully submit that the subject specification provides adequate guidance for the skilled person to identify and use appropriate cells, without resort to undue experimentation.

The Action also indicates that the subject specification does not provide sufficient guidance for conferring conditional immortality to cells (*e.g.*, via the temperature sensitive oncogene (tsA58)). As taught in the specification, such conditionally immortal cells can be readily prepared by transduction of an oncogene into a cell (see, for example, page 6 of the specification). As taught at

page 7, lines 1-7, of the specification, the use of non-human transgenic animals is but one method for obtaining conditionally immortalized cells. Conditional immortality is described on page 5, last paragraph, and pages 6 and 7 of the specification, and it is clear that the cells remain immortal (undifferentiated and continuously dividing) under one set of conditions, but can be induced to mature and differentiate (losing immortality) by a change in conditions. The Frederiksen *et al.* publication (*Neuron*, Vol. 1, 439-448, 1988) and Jat *et al.* publication (*Proc. Natl. Acad. Sci. USA*, 88:5096-5100, June 1991), which accompanied the Amendments submitted on September 30, 2002 and March 20, 2003, respectively, show that methods for achieving conditional immortality using, for example, the temperature-sensitive SV40 oncogene, were known in the art even in 1988. The background section of the Snyder *et al.* patent also highlights methods (both epigenetic and genetic) for immortalizing cells that are not dependent on the large T antigen temperature-sensitive oncogene (see column 1, lines 31-43 of the Snyder *et al.* patent). Therefore, the applicants respectfully assert that the specification fully enables human, pluripotent, nestin-positive neuroepithelial cells that have been genetically modified to be conditionally immortal, as recited in the currently pending claims.

As observed at page 10 of the Office Action, the human cells used in the experiment described in Exhibit D express both nestin (intermediate filament marker) and musashi 1. As indicated in Exhibit D, nestin and musashi 1 are both phenotypic markers for neuroepithelial stem cells. The musashi 1 marker was more recently identified than nestin and, hence, merely confirms the neural epithelial status of the cells, as determined by nestin expression. Thus, one of ordinary skill in the art would appreciate that musashi 1 expression does not represent a characterizing feature of the cells that had to be identified before the invention could be carried out; demonstrating the expression of nestin by the cells, as taught in the specification, is sufficient.

The applicants respectfully submit that a person skilled in the art, having the benefit of the specification's disclosure, could readily make and use the claimed invention without resort to undue experimentation. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

Claims 57-62, 64, and 68-75 are rejected under the judicially created doctrine of "obviousness-type" double patenting as being unpatentable over claims 1-15 of U.S. Patent No. 6,569,421 in view of Snyder (U.S. Patent No. 5,958,767). The applicants have submitted herewith a

Terminal Disclaimer executed by the undersigned attorney of record and in compliance with the requirements of 37 CFR §1.321(c), which obviates the rejection based on U.S. Patent No. 6,569,421. This Terminal Disclaimer is being submitted solely to expedite prosecution of the subject application to completion and should not be construed as an admission that the claimed subject matter is obvious over the claims in the cited patent. Accordingly, reconsideration and withdrawal of the "obviousness-type" double patenting rejection is respectfully requested.

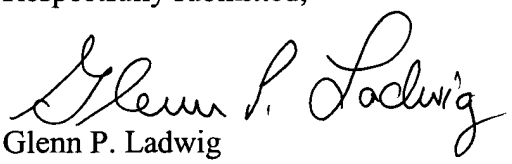
In addition, claims 57-62, 64, and 68-75 are provisionally rejected under the judicially created doctrine of "obviousness-type" double patenting as being unpatentable over the claims of copending U.S. application serial nos. 09/672,606, 10/342,692, and 10/376,119. The applicants respectfully submit that application serial no. 09/672,606 is currently abandoned; therefore, this aspect of the double patenting rejection is moot. The applicants respectfully submit that the claims of the subject application are not obvious over the claims of U.S. application serial nos. 10/342,692 and 10/376,119.

In view of the foregoing remarks and amendments to the claims, the applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

The applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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Attachments: Petition and Fee for Extension of Time;
Terminal Disclaimer;
Notice of Acceptance from U.S. application serial no. 09/043,061;
Copy of Return Receipt Post Card showing submission of IDS and Form PTO-1449 on February 14, 2001 and receipt by the U.S. Patent Office on February 20, 2001; and
U.S. Patent No. 6,528,306 (Snyder *et al.*)